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Chronic ulcerative colitis and colorectal cancer

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Abstract: One of the most important consequences of chronically active ulcerative colitis (UC) or Crohn's disease (CD) - the two major forms of inflammatory bowel disease (IBD) - is the development of colorectal cancer (CRC). An increased risk for the occurrence of CRC in up to 30% of affected patients after 35 years of UC has been reported. Recent evidence from population based studies indicates a lower risk. Nevertheless the incidence is still significantly increased as compared to individuals without chronic colitis. Colitis-associated CRC (CAC) does not display the adenoma-carcinoma sequence which is typical for sporadic CRC and the pathophysiology appears to be different. Chronic inflammation and the increased turnover of epithelial cells contribute to the development of low- and high-grade dysplasia which may further transform into CAC. Reactive oxygen species (ROS) generated by the inflammatory infiltrate are thought to contribute to the generation of dysplastic lesions. In sporadic CRC the sequence of mutations that finally lead to malignancy involves early activation of Wnt/-catenin pathway (in 90% of cases) including mutations in adenomatous polyposis coli (APC) tumor suppressor gene, its regulating kinase GSK3 and -catenin itself. -catenin mutations are rarer in CAC and mutations in APC occur rather late during the disease progression, whereas there are earlier mutations in p53 and K-ras. Recent data indicate that the intestinal microbiome and its interaction with a functionally impaired mucosal barrier may also play a role in CAC development. CACs frequently show aggressive growth and early metastases. The treatment of CAC in patients with colitis always includes proctocolectomy with ileoanal anastomosis as meta- or synchronous lesions are frequent.

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Chronic ulcerative colitis and colorectal cancer

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Abstract

One of the most important consequences of chronically active ulcerative colitis (UC) or Crohn's disease (CD) – the two major forms of inflammatory bowel disease (IBD) - is the development of colorectal cancer (CRC). An increased risk for the occurrence of CRC in up to 30% of affected patients after 35 years of UC has been reported. Recent evidence from population based studies indicates a lower risk. Nevertheless the incidence is still significantly increased as compared to individuals without chronic colitis. Colitis-associated CRC (CAC) does not display the adenoma-carcinoma sequence which is typical for sporadic CRC and the pathophysiology appears to be different. Chronic inflammation and the increased turnover of epithelial cells contribute to the development of low- and high-grade dysplasia which may further transform into CAC. Reactive oxygen species (ROS) generated by the inflammatory infiltrate are thought to contribute to the generation of dysplastic lesions. In sporadic CRC the sequence of mutations that finally lead to malignancy involves early activation of Wnt/ β -catenin pathway (in 90 % of cases) including mutations in adenomatous polyposis coli (APC) tumor suppressor gene, its regulating kinase GSK3 β and β -catenin itself. β -catenin mutations are rarer in CAC and mutations in APC occur rather late during the disease progression, whereas there are earlier mutations in p53 and K-ras. Recent data indicate that the intestinal microbiome and its interaction with a functionally impaired mucosal barrier may also play a role in CAC development. CACs frequently show aggressive growth and early metastases. The treatment of CAC in patients with colitis always includes proctocolectomy with ileoanal anastomosis as meta- or synchronous lesions are frequent.

Key Words: ulcerative colitis; colorectal cancer; cancer risk; Crohn's disease; inflammation-associated cancer; dysplasia; intraepithelial neoplasia

Colorectal cancer in patients with chronic colitis: What is the risk?

Ulcerative colitis (UC) is one of the two major forms of chronic inflammatory bowel diseases a relapsing inflammation of the colonic mucosa with variable extension from the rectum towards the cecum. The inflammation in ulcerative colitis is limited to the mucosal layer. It normally begins in the rectum where usually the highest activity of inflammation is found. In contrast, in Crohn's disease, the second major form on inflammatory bowel disease, the inflammation is transmural affecting all layers of the gut wall. Involved gut segments show a discontinuous pattern frequently affecting the terminal ileum and also the colon. Both diseases usually occur in young adults between 20 and 30 years of age. However, disease onset may already be during childhood or be delayed to older ages. Due to the increasing incidence the number of young adults suffering from chronic colitis still is on the rise [1; 2; 3; 4; 5; 6; 7; 8].

The standard step-up treatment of UC starts with 5-aminosalicylic acid (which may have cancer-preventive activity). If the treatment response is not sufficient, steroids, immunosuppressants or biologicals (such as anti-TNF antibodies and in the near future anti-integrin antibodies) may be applied. Despite these treatment options there are patients that experience frequent flares of inflammation or develop a treatment resistant disease with chronic inflammatory activity. In those patients, when no complete remission ("mucosal healing") can be achieved the continuous inflammation repeatedly destroys the epithelial surface of the mucosa. Crypt abscesses with crypt distortions are found and ongoing repair mechanisms are a histological hallmark. The loss of epithelial cells has to be compensated by increased epithelial proliferation as a repair mechanism which may finally be uncontrolled leading to CAC.

Subsequently, the risk of CAC is increased after long disease duration, especially in patients with chronic active disease [9; 10]. In older studies the risk for CAC in UC patients was reported to be around 7% at 20 years after onset of disease [11; 12; 13], 7-14% at 25 years [14; 15] and as high as 30% after 35 years [16] (Figure 1). This would mean that the life-time risk in any UC patient would be 2-4 times the risk of the control population which is around 5% [10]. However, risk stratification seems to be possible with respect to specific characteristics of the disease. Eaden and co-workers published a meta-analysis on the risk of CAC in UC patients in 2001 based on 116 studies and on 54.478 patients. They confirmed that there is an increased risk for CAC in pancolitis as compared to left sided colitis [16] (Figure 1). The overall prevalence of CAC in any patient with UC was shown to be 3.7%, in patients with pancolitis it was 5.4% [16]. In ulcerative proctitis the CAC risk appears not to be increased.

More recent data indicate that the risk of CAC may be lower. Jess et al. used a population-based nationwide registry and did find no increase in the incidence of CRC in UC patients at all [17] (Figure 1). Neither the overall cancer risk nor the CAC risks were increased after a median of 19 years of follow-up evaluation. This surprising finding, however, may be due to the higher rates of colectomy in UC patients in Denmark [17]. Using data from a large cohort of patients with extensive UC (600 patients with 30 years of observation period) Rutter and co-workers reported cumulative incidences of CAC of 2.5% at 20 years of colitis duration, 7.6% at 30 years, and 10.8% at 40 years [18] (Figure 1) indicating only a 1.5 to 2-fold increased risk for CRC as compared with the non-UC population. Only 30/600 patients (5%) developed CAC [18] in this cohort. A recent Swedish study including 7,607 patients with UC diagnosed between 1954 and 1989 analysed the frequency of CAC through

2004. The study indicates that over the past 35 years the risk of death from CAC declined markedly [19] (Table 1). A further recent study by Manninen et al. could confirm an only slightly increased risk for CAC in UC patients in a Finnish cohort [20]. The CAC risk was 3.09 (CI 1.50-5.75) for pancolitis and 3.62 (CI 2.00-11.87) for CD colitis [20]. However, 52% of the eleven detected CAC already were TNM stage 3 or 4 [20]. Similar findings were obtained within the GETAID study [21] and in an Australian cohort [22]. Recently Jess and co-workers performed a meta-analysis on population based studies [23]. They found that an average of 1.6% of patients with UC was diagnosed with CAC during 14 years of follow-up [23]. Men with UC had a greater risk of CAC as compared to women. In the population-based (unbiased and unselected cohorts) the diagnosis of UC increased the risk of CRC 2.4-fold as compared to the healthy population (which is clearly lower as compared to the Eaden data). A direct comparison of the Eaden- and Jess-data makes the differences obvious: In contrast to the above mentioned cumulative incidences of CAC of 2% at 10 years and 8% at 20 years of follow-up for any patient with UC, these figures were only 0.4% and 1.1%–5.3%, respectively, in the recent meta-analysis [23] (Figure 1).

The analysis on non-population based data derived from specialized centers may have introduced some selection-bias into the analyses. However, in a recent analysis of cases in the Swiss IBD cohort study which includes more than 50% of patients from specialized tertiary centers the rate of CAC was comparable to the low incidence reported in recent publications (own unpublished data). Thus the decreased incidence of CAC is more likely due to a better control of inflammation by improved medical therapy and higher rates of mucosal healing. However, evidence remains indirect.

Importantly, the risk to develop CAC is further increased in patients with primarily sclerosing cholangitis (PSC) [24; 25; 26; 27; 28; 29; 30; 31]. The mechanism behind that is unclear. Many hypotheses have been generated; however, none has been supported with sufficient clinical or experimental evidence.

CRC in chronic colitis: What is the role of inflammation?

In contrast to sporadic CRC the permanent stimulation of epithelial proliferation in an inflammatory environment is believed to play an important role for the pathogenesis of CAC in patients with chronic colitis [10; 20]. A typical adenoma-carcinoma sequence is not found. UC patients may have low grade epithelial dysplasia in typical adenomatous lesions. However, dysplasia found in “dysplasia associated lesions or masses” (DALM) or in areas without any macroscopically visible mucosal alteration is believed to be the origin CAC [32; 33; 34]. Such a lesion may require colectomy whereas low grade dysplasia in an ALM lesion (i.e. a typical adenoma) may be “treated as usual” [34; 35; 36; 37].

An argument for the important role of inflammation for CAC development is the fact that CAC risk increases with the duration of the disease and correlates positively with the severity of inflammation and extend of the disease as mentioned above [10; 16; 20; 32; 38; 39] . Unfortunately, there is no uniform and general accepted definition of “disease-duration”. Onset of symptoms has generally been used as starting point for disease-duration in the studies that have identified this parameter as a risk factor [40]. Based on the meta-analysis by Eaden et al. it is assumed that the risk for CAC begins to increase 8 – 10 years after onset of inflammation [16]. This indicates that longer duration of inflammation promotes CAC

development. However, also very early CAC occurrence has been reported in some cases of colitis patients [41]. Persistent histological inflammation is a prerequisite for the development of CAC [10; 20; 32; 42]. As mentioned, the CAC risk is lower in left sided colitis and almost absent in proctitis – which in fact is somewhat surprising. The inflammation is most severe in the rectum and thus the highest levels of cytokines and ROS may be found there. Why this is not followed by a predominant localization of CACs in the rectum – even in proctitis – remains unclear. Even in patients with pancolitis most lesions have been reported to be left-sided [43; 44] – however, there are also reports on a random distribution over the whole colon [45].

The crucial pathophysiological role of mucosal inflammation is highlighted by the fact that successful anti-inflammatory treatment (e.g. with 5-ASA or thiopurines) may reduce the risk to develop CAC [46; 47; 48; 49; 50; 51]. Whereas the benefit of anti-inflammatory treatment and subsequent mucosal healing overall is quite clear [52; 53], conflicting data have been obtained for single agents such as 5-ASA [54; 55; 56; 57] .

CRC in chronic colitis: Mutations and molecular mechanisms

Pathogenetic features detected in patients with sporadic CRC such as chromosome instability, microsatellite instability, and DNA hypermethylation also can be found in patients with CAC [10; 45; 58; 59; 60; 61]. However, in contrast to patients with sporadic CRC cells of the inflamed mucosa-areas may harbour such changes before dysplasia or CAC can be detected [59, Li, 2012 #2919; 62]. Microsatellite instability, telomere shortening and chromosomal instability are regarded to occur as the molecular responses to genomic stress [62].

Inflammation alone may be sufficient to induce these changes. They may not necessarily lead to CAC making the early diagnosis of relevant early changes finally leading to CAC very difficult [63; 64; 65]. As mentioned above CAC does not show a typical adenoma-carcinoma sequence but may develop from low-grade dysplasia to high-grade dysplasia and finally CAC [66].

Inflammation is associated with the production of reactive oxygen species (ROS) which in turn may cause cellular damage that can become oncogenic [67]. Thus, ROS production has been considered to be an important factor for the pathogenesis of chronic CAC [68; 69] (Figure 2). IBD has been discussed considered to be an “oxyradical overload” disease [70; 71; 72]. The deletion of ROS regulating genes such as the immediate early response gene X-1 (IEX-1) in a mouse model of colitis and colitis-associated cancer (azoxymethane/dextrane sodium sulfate [AOM/DSS] model) was followed by reduced inflammatory responses and CRC development [73]. However, with respect to the pathophysiological role of ROS the question arises why CAC does not always develop in the area of highest ROS production (i.e. in the rectum of patients with UC or in the terminal ileum in patient suffering from CD)

Free radicals may either affect metabolic processes regulating DNA synthesis, RNA synthesis, protein assembly or DNA repair [71]. ROS may alter the function of genes and proteins that are crucial for the homeostasis of cell proliferation (necessary for tissue repair) and apoptosis (anoikis). When colonic epithelial cells lose their cell-cell or cell-matrix contacts they usually die from apoptosis/anoikis [74; 75]. For the closure of ulcers and epithelial defects in the colon of affected patients it may be important to avoid the inescapable induction of apoptosis, which consecutively

may in turn be associated with a lack of efficient control mechanisms for exaggerated cell proliferation.

Similar to sporadic CRC colitis-associated high grade dysplasia or CAC develops with a sequence of molecular events on a cellular level; however, the sequence of events is different between sporadic CRC and CAC. High grade dysplasia and CAC development in patients with chronic colitis frequently occurs multifocally indicating that similar events take place in different areas of the affected mucosa [76; 77]. Similar to sporadic CRC in CAC chromosome instability and microsatellite instability occur in 85% and 15% of cases, respectively [78]. However, as mentioned the sequence of molecular events on the cellular levels differs between both entities. Whereas in sporadic CRC the loss of function of the adenomatous polyposis coli (APC) protein is an early event already occurring during the formation of early adenoma it is less frequent and occurs late in the pathogenesis of CAC [79; 80 Umetani, 1999 # 357] (Figure 2). As APC is essential for maintenance of mucosal and epithelial homeostasis an early loss of APC function may cause anoikis of epithelial cells thus preventing the development of CACs [81].

p53-mutations, p53-loss of heterozygosity (LOH) or -loss of function are early and important events in the pathogenesis of CAC, whereas they occurs late in sporadic CRC (usually during transition from late adenoma to CRC) [82; 83; 84; 85; 86] (Figure 2). Deletion of p53 is found in up to 85% of CACs [87; 88; 89]. p53 mutations can be detected in chronically inflamed colon mucosa before any dysplasia develops (up to 50% of chronically inflamed patients) [84] (Figure 2). Mutant mutp53 prolongs TNF-alpha-induced NF-kappaB activation which in mice harboring a germline p53 mutation causes severe tissue damage and a higher risk to CAC [85].

Mutated p53 caused a rapid development of high grade dysplasia, rapidly progressing to invasive carcinoma [85]

DNA hypermethylation also is a typical feature of CAC [90]. Methylation of CpG islands in several genes can be found in chronically inflamed mucosa without visible dysplasia or lesion [61; 91]. Genes that are frequently hyper-methylated in chronic colitis-associated CRC are hMLH1 (in up to 46%, [92]), the cell cycle inhibitor p16INK4a and its promoter (up to 100%) [93] or p14ARF (33-60%, [94]).

Another important factor in the pathogenesis of CAC is the intestinal microflora. In animal models of colitis the commensal flora or specific bacteria are necessary for the development of inflammation and for the induction of CAC [95; 96]. Mice raised under germ-free conditions usually neither develop inflammation nor CAC. In IL-10 deficient animals the time point of occurrence of inflammation is dependent on the composition of the colonic microflora and CAC only develops in genetically identical mice in some animal facilities indicating the crucial influence of the microflora.

In a recent study by the group of Jobin and co-workers the intestinal microbiota was identified as a target of inflammation that finally affects the initiation and progression of CAC. In interleukin (IL)-10–deficient mice a modification of the microbiome was found upon spontaneous development of colitis. Colonization of these mice with specific bacterial strains such as the commensal *Escherichia coli* NC101 supported the development of invasive inflammation induced CAC in azoxymethane (AOM)–treated IL-10 deficient mice [97; 98]. In addition, epithelial damage during inflammation and the translocation of bacteria across the epithelial barrier further may support CAC development. In a mouse model with defective intestinal barrier function at tumour sites the translocation of bacterial products was

followed by activation of myeloid cells, induction of IL-23 and IL-17 secretion and promotion of tumour growth [99]. IL-17 producing T-cells promote CAC tumorigenesis [99]. Further, IL-23 dependent signalling may promote CAC growth and progression [99]. In a mouse model of CAC IL-23 was mainly produced by tumour-associated myeloid cells which could be activated by microbial products in vivo again highlighting the potential role of the intestinal microbiota.

Colorectal cancer in chronic colitis: What is the prognosis?

Unfortunately CAC frequently is detected at late stages. Kavanagh and co-workers found fifty percent (11/22) of UC patients and 71 % (5/7) of CD patients with CAC from a cohort of 2,843 inflammatory bowel disease patients had nodal or distant metastases at presentation [45]. Similar data have been reported from the Mayo Clinic [100]. CAC patients are younger, have more frequently multiple cancerous lesions, and higher proportions of mucinous or signet ring cell carcinomas [101]. In animal models of CAC cell growth is faster in inflamed areas [102]. This may contribute to the aggressiveness. The advanced stage at presentation causes less favourable outcome of CAC in IBD patients. 5-year survival rates for CAC ranges from 19–55% [45; 101; 103; 104; 105; 106]. The long term prognosis of CAC is even worse, when patients with the same tumour stage are compared: In a recent study stage III CAC patients had a poorer survival rate than patients with sporadic CRC (43.3% versus 57.4%, $P = 0.0320$) [101]. Encouragingly patients diagnosed at an early stage of CAC did not differ in their outcome from the sporadic CRC group [101]. This may underline the importance of surveillance colonoscopy for patients with chronic active colitis. Whereas this seems to be obvious the evidence is still weak [107]. The best performance of surveillance colonoscopy is discussed in many

guidelines and reviews and there is no space to do this here [35; 108; 109; 110; 111; 112].

Surgical morbidity in patients with CAC is high despite the lower age at diagnosis as compared to sporadic CRC which may partially be caused by the underlying inflammatory disease [45].

As evidence is quite good that mucosal healing may prevent CAC development in chronic colitis patients this treatment goal is more and more adopted in clinical practice. Together with efficient surveillance strategies this seems to decrease the incidence of CAC in some countries [113]. Nevertheless it will be important to better understand the specific pathophysiology of these tumours to provide optimal targeted chemo-therapy for the patient group that will still develop CAC.

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Figure legends

Figure 1: **Risk for CRC in UC patients with respect to disease duration.**

Comparisons of the meta-analyses/cohort studies by Eaden et al (6), Rutter et al (8) and Jess et al (10). There is a clear decrease of the risk evaluation between the studies. A trend for lower risk is observed in recent years.

Figure 2: **Pathways of CRC formation in sporadic cancer and chronic colitis associated cancer.** The sequence of molecular events on the cellular levels differs. Whereas in sporadic CRC the loss of function of the adenomatous polyposis coli (APC) protein is an early event, it is less frequent and occurs late in the pathogenesis of chronic colitis-associated dysplasia and CRC. p53-mutations or loss of function are early events in chronic colitis associated CRC, whereas they occur late in sporadic CRC during transition from late adenoma to CRC.

Table 1:

	10 years	20 years	30 years
Pancolitis	1.5	3.8	7.6
UC	1	2.3	5.2
CD	0.5	1.4	2.2

Table 1: Risk of colorectal cancer in 3 population based Swedish cohorts (1954 – 1989) including 7 607 patients with IBD (198 227 patient-years). 196 CRCs were found in 188 patients. (Söderlund S, Brandt L, Lapidus A, Karlen P, Broström O, Löfberg O, Ekbom A, Askling J. Decreasing Time-Trends of Colorectal Cancer in a Large Cohort of Patients With Inflammatory Bowel Disease, Gastroenterology 2009;136:1561-1567, Ref 9)